PA NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
ROYAUME-UNI

Date of mailing (day/month/year)
08 October 2001 (08.10.01)

Applicant's or agent's file reference
P15770WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02216

International filing date (day/month/year)
19 June 2000 (19.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ML LABORATORIES
17 Hanover Square
London W1R 9AJ
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ML LABORATORIES PLC
17 Hanover Square
London W1R 9AJ
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
R. Raissi
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
GRANDE BRETAGNE

~~12.2001 06279~~

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.09.2001
Applicant's or agent's file reference: P15770WO / RLD.	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02216	19/06/2000	18/06/1999

Applicant
ML LABORATORIES et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Gallego, A Tel.+49 89 2399-8102

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

18.SEP.2001* 1284

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P15770WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02216	19/06/2000	18/06/1999
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant ML LABORATORIES et al.		

~~14.SEP.2001 062770~~

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/01/2001	12.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Döpfer, K-P Telephone No. +49 89 2399 8547

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02216

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-11 as originally filed

Claims, No.:

1-23 with telefax of 31/08/2001

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item I

Basis of the report

1. The amended claims 1-23 are in accordance with the requirements of Article 34(2)(b) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: WO 98 56424 A (CASSIDY JAMES ;DUNCAN RUTH (GB); GERMAN LISA (GB); HIRST DALE (GB)) 17 December 1998 (1998-12-17)

D2: EP-A-0 477 931 (MERCIAN CORP) 1 April 1992 (1992-04-01)

D3: WO 96 35720 A (KHAN RIAZ ;KONOWICZ A PAUL (GB); FIDIA ADVANCED BIOPOLYMERS SRL (I) 14 November 1996 (1996-11-14)

D4: ARRANZ F ET AL: 'ADDUCTS OF SUCCINYLATED DEXTRAN-BENZOCAINE. SYNTHESIS AND CONTROLLED RELEASE BEHAVIOUR' MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS,CH,HUTHIG UND WEPF VERLAG. BASEL, vol. 13, no. 9, 1 September 1992 (1992-09-01), pages 403-407, XP000301002

D5: WO 95 05199 A (DEXTRAN PRODUCTS LTD) 23 February 1995 (1995-02-23)

D6: SHEN ET AL: 'cis-Aconityl spacer between daunomycin and macromolecular carriers: a model of pH-sensitive linkage releasing drug from a lysosomotropic conjugate' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,US,ACADEMIC PRESS INC. ORLANDO, FL, vol. 102, no. 3, 15 October 1981 (1981-10-15), pages 1048-1054, XP002114459 ISSN: 0006-291X

D7: HRECZUK-HIRST D.H. ET AL: 'Synthesis and characterisation of dextrin-doxorubicin conjugates: A new anticancer treatment' PROCEEDINGS OF THE CONTROLLED RELEASE SOCIETY, 1999, VOL. -, NO. 26, PAGE(S) 1086-1087, XP001002321 United States

2. The present application relates to conjugates of anti-cancer drugs (e.g. doxorubicin) with modified dextrin polymers, the modification is a succinoylation by at least 20mol%.

2.1 *Novelty and Inventive Step (Article 33(2)(3) PCT)*

Prior art document D1 discloses conjugates of anticancer drugs with succinoylated dextrin (see page 2, line 15 - page 5, line 2; cf in particular expls. 3.1, 3.2, 3.4: doxorubicin-succinoylated dextrin).

D2 addresses conjugates adriamycin with dextrin which *inter alia* has been modified by succinoylation (see page 3, formula (I); claims 1, 7-10).

D3 refers to succinoylated hyaluronic acid derivatives which are use in the treatment of osteoarticular disorders. No anti-cancer drugs are mentioned. No hint is given to dextrin. Therefore, D3 is considered not relevant for the assessment of novelty and inventive step of the present application.

D4 discloses the synthesis and release behaviour of adducts of succinylated dextran-benzocaine. This document is considered representing background art because the targeting and stability requirements of anti-cancer conjugates differ remarkably from those for anaesthetics.

D5 relates to the synthesis of conjugates dextrin/dextran with AZT by means of succinyl anhydride. The succinic moiety does not serve as pendent group in the sense of dextrin modification but as linker between the carbohydrate and the drug. Thus, the teaching of this document is not considered as particularly relevant.

D6 teaches the influence of spacers (cis-aconitoyl, maleyl) upon the pH-dependent release of daunomycin from its macromolecular carriers like aminoethyl polyacrylamide and poly(D-lysine). Succinoyl as pendent moiety is not mentioned, neither is the influence of pendent groups on the stability of conjugates. This document is not regarded as being relevant since no dextrin

conjugates are disclosed or even discussed.

D7 does not form part of the prior art according to Rule 64 PCT because the priority claim of the present application has been found valid.

None of the prior art documents disclose polymer drug conjugates comprising dextrin polymers being modified by at least 20mol% succinoyl groups.

D1 is considered representing the closest prior art. Taking the teaching of this document into consideration, the problem underlying the present application is to be regarded as to provide further modification of the known conjugates. The solution are the higher succinoylated conjugates of the present application. These conjugates with higher modification grades show an increased stability (see examples 2-4 and figures 1-3, see table 3) *in vivo* and *in vitro*. Furthermore, the increase in polymer stability when used as an imaging agent cannot be derive from the teachings of the prior art either. Thus, the subject-matter of the present application meets the requirements of novelty and inventive step.

2.2 *Industrial applicability (Article 33(4) PCT*

The subject-matter of present claims 1-21 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Claims 22 and 23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this documents identified therein.

PATENT COOPERATION TREATY

York

17.OCT.2001*064906

PCT

From the INTERNATIONAL BUREAU

To:

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
ROYAUME-UNI

19.OCT.2001* 1880

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
08 October 2001 (08.10.01)	
Applicant's or agent's file reference P15770WO KOD	
International application No. PCT/GB00/02216	**International filing date** (day/month/year) 19 June 2000 (19.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ML LABORATORIES 17 Hanover Square London W1R 9AJ United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ML LABORATORIES PLC 17 Hanover Square London W1R 9AJ United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. Raissi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

RCD

PATENT COOPERATION TREATY

17.[redacted].2001* - 21

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
GRANDE BRETAGNE

16. JUL. 2001 059219

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	12.07.2001
Applicant's or agent's file reference: P15770WO	**REPLY DUE** **within 1 month(s) and 15 days** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02216	19/06/2000	18/06/1999

International Patent Classification (IPC) or both national classification and IPC
A61K47/48

Applicant
ML LABORATORIES et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 18/10/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Döpfer, K-P

Formalities officer (incl. extension of time limits)
Gallego, A
Telephone No. +49 89 2399 8102

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4, 10-14 No
Inventive step (IS)	Claims	1-14 No
Industrial applicability (IA)	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item I

Basis of the opinion

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: WO 98 56424 A (CASSIDY JAMES ;DUNCAN RUTH (GB); GERMAN LISA (GB); HIRST DALE (GB)) 17 December 1998 (1998-12-17)

D2: EP-A-0 477 931 (MERCIAN CORP) 1 April 1992 (1992-04-01)

D3: WO 96 35720 A (KHAN RIAZ ;KONOWICZ A PAUL (GB); FIDIA ADVANCED BIOPOLYMERS SRL (I) 14 November 1996 (1996-11-14)

D4: WO 95 05199 A (DEXTRAN PRODUCTS LTD) 23 February 1995 (1995-02-23)

D5: ARRANZ F ET AL: 'ADDUCTS OF SUCCINYLATED DEXTRAN-BENZOCAINE. SYNTHESIS AND CONTROLLED RELEASE BEHAVIOUR' MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS,CH,HUTHIG UND WEPF VERLAG. BASEL, vol. 13, no. 9, 1 September 1992 (1992-09-01), pages 403-407, XP000301002

D6: SHEN ET AL: 'cis-Aconityl spacer between daunomycin and macromolecular carriers: a model of pH-sensitive linkage releasing drug from a lysosomotropic conjugate' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,US,ACADEMIC PRESS INC. ORLANDO, FL, vol. 102, no. 3, 15 October 1981 (1981-10-15), pages 1048-1054, XP002114459 ISSN: 0006-291X

D7: HRECZUK-HIRST D.H. ET AL: 'Synthesis and characterisation of dextrin-doxorubicin conjugates: A new anticancer treatment' PROCEEDINGS OF THE CONTROLLED RELEASE SOCIETY, 1999, VOL. -, NO. 26, PAGE(S) 1086-1087, XP001002321 United States

2. The present application relates to conjugates of anti-cancer drugs (e.g. doxorubicin) with modified dextrin polymers.

2.1 *Novelty and Inventive Step (Article 33(2)(3) PCT)*

Prior art document D1 discloses conjugates of anticancer drugs with succinoylated dextrin (see page 2, line 15 - page 5, line 2; cf in particular expls. 3.1, 3.2, 3.4: doxorubicin-succinoylated dextrin).

The disclosure of this document is considered pertinent for the novelty of present claims 1-4 and 10-14.

D2 addresses conjugates adriamycin with dextrin which *inter alia* has been modified by succinoylation (see page 3, formula (I); claims 1, 7-10). This subject-matter is pertinent for the novelty of present claims 1, 2, 4, 10-14.

D3 refers to succinoylated hyaluronic acid derivatives which are use in the treatment of osteoarticular disorders. No anti-cancer drugs are mentioned. No hint is given to dextrin. Therefore, D3 is considered not relevant for the assessment of novelty and inventive step of the present application.

D4 discloses the synthesis and release behaviour of adducts of succinylated dextran-benzocaine. This document is considered representing background art because the targeting and stability requirements of anti-cancer conjugates differ remarkably from those for anaesthetics.

D5 relates to the synthesis of conjugates dextrin/dextran with AZT by means of succinyl anhydride. The succinic moiety does not serve as pendent group in the sense of dextrin modification but as linker between the carbohydrate and the drug. Thus, the teaching of this document is not considered as particularly relevant.

D6 teaches the influence of spacers (cis-aconitoyl, maleyl) upon the pH-dependent release of daunomycin from its macromolecular carriers like aminoethyl polyacrylamide and poly(D-lysine). Succinoyl as pendent moiety is not mentioned, neither is the influence of pendent groups on the stability of

conjugates. This document is not regarded as being relevant since no dextrin conjugates are disclosed or even discussed.

D7 does not form part of the prior art according to Rule 64 PCT because the priority claim of the present application has been found valid.

D1 is considered representing the closest prior art. Taking the teaching of this document into consideration, the problem underlying the present application is to be regarded as to provide further modification of the known conjugates. The solution are the higher succinoylated conjugates of present claims 5-9. These conjugates with higher modification grades do not exhibit any surprising effects which could establish an inventive step. Accordingly, all claims 1-14 lack inventive step in view of the pertinent prior art.

2.2 *Industrial applicability (Article 33(4) PCT*

The subject-matter of present claims 1-13 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item VII
Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this documents identified therein.

PATENT COOPERATION TREATY

PCT 01*05659

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
Harrison Goddard Foote
Tower House
Merrion Way
Leeds LS2 8PA
UNITED KINGDOM

Date of mailing *(day/month/year)* 08/06/2001	
Applicant's or agent's file reference P15770WO RCD	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 00/02216	International filing date *(day/month/year)* 19/06/2000

Applicant

ML LABORATORIES et al.

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Joannes Vergoosen

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/78355 A3

(54) Title: BIOLOGICALLY ACTIVE MATERIALS

(57) Abstract: The invention relates to a polymer drug conjugate for the treatment of cancer comprising a succinoylated dextrin wherein said succinoylation enhances the *in vivo* stability of said conjugate.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/02216

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K51/06 //A61K101:02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, PAJ, WPI Data, EPO-Internal, MEDLINE, CANCERLIT, CHEM ABS Data, DISSERTATION ABS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56424 A (CASSIDY JAMES ;DUNCAN RUTH (GB); GERMAN LISA (GB); HIRST DALE (GB)) 17 December 1998 (1998-12-17) examples 3.1,3.2,4 figures 3A,3B	1-14
X	EP 0 477 931 A (MERCIAN CORP) 1 April 1992 (1992-04-01) examples	1-14
Y	WO 96 35720 A (KHAN RIAZ ;KONOWICZ A PAUL (GB); FIDIA ADVANCED BIOPOLYMERS SRL (I)) 14 November 1996 (1996-11-14) page 10, line 1 -page 11, line 13	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2001	08/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dullaart, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/02216

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ARRANZ F ET AL: "ADDUCTS OF SUCCINYLATED DEXTRAN-BENZOCAINE. SYNTHESIS AND CONTROLLED RELEASE BEHAVIOUR" MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS,CH,HUTHIG UND WEPF VERLAG. BASEL, vol. 13, no. 9, 1 September 1992 (1992-09-01), pages 403-407, XP000301002 page 403, paragraph INTRODUCTION page 406 ---	1-14
Y	WO 95 05199 A (DEXTRAN PRODUCTS LTD) 23 February 1995 (1995-02-23) claims ---	1-14
Y	SHEN ET AL: "cis-Aconityl spacer between daunomycin and macromolecular carriers: a model of pH-sensitive linkage releasing drug from a lysosomotropic conjugate" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,US,ACADEMIC PRESS INC. ORLANDO, FL, vol. 102, no. 3, 15 October 1981 (1981-10-15), pages 1048-1054, XP002114459 ISSN: 0006-291X abstract page 1049 ---	1-14
P,X	HRECZUK-HIRST D.H. ET AL: "Synthesis and characterisation of dextrin-doxorubicin conjugates: A new anticancer treatment" PROCEEDINGS OF THE CONTROLLED RELEASE SOCIETY, 1999, VOL. -, NO. 26, PAGE(S) 1086-1087, XP001002321 United States page 1087 -----	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02216

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0998303 A	10-05-2000
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WO 9635720 A	14-11-1996	IT PD950090 A	11-11-1996
		AU 695512 B	13-08-1998
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		JP 11504668 T	27-04-1999
		US 6017901 A	25-01-2000
		AT 183206 T	15-08-1999
		CA 2220682 A	14-11-1996
		ES 2137694 T	16-12-1999
WO 9505199 A	23-02-1995	NONE	

CLAIMS

1. A polymer drug conjugate comprising:

i) at least one anti-cancer drug; and

ii) a dextrin polymer

characterised in that said dextrin polymer is modified by addition of pendent groups so that the stability of the polymer drug conjugate is enhanced.

2. A polymer drug conjugate according to Claim 1, wherein said modification is by the addition of pendent groups selected from: negatively charged groups, neutral groups or positively charged groups.

3. A polymer drug conjugate according to Claim 1 or 2, wherein said modification is by the addition of quaternary ammonium groups.

4. A polymer drug conjugate according to Claims 1 or 2, wherein said dextrin modification is succinoylation.

5. A polymer drug conjugate according to Claim 4, wherein said dextrin is succinoylated to at least 20mol%.

6. A polymer drug conjugate according to claim 4, wherein said dextrin is succinoylated to at least 30mol%.

7. A polymer drug conjugate according to Claim 6, wherein said dextrin is succinoylated from 30% to 40mol%.

8. A polymer drug conjugate according to Claim 7, wherein said dextrin is succinoylated from 32% to 36%.

9. A polymer drug conjugate according to Claim 8 wherein said dextrin is succinoylated to about 34mol%.

10. A polymer drug conjugate according to Claims 1 - 9, wherein said anti cancer agent is selected from: cyclophosphamide; melphalan; carmusline; methotrexate, 5-fluorouracil; cytarabine; mercaptopurine; anthracyclines; daunorubicin, doxorubicin; epirubicin; vinca alkaloids; vinblastin; vincristine; dactinomycin; mitomycin C; taxol; L-asparaginase; G-CSF; cisplatin; carboplatin.

11. A pharmaceutical composition comprising a polymer drug conjugate according to any preceding Claims.

12. A pharmaceutical composition according to Claim 11 wherein said composition comprises a diluent, carrier or excipient.

13. The use of a polymer drug conjugate according to Claims 1 – 9 for the manufacture of a medicament for the treatment of cancer.

14. A method of treatment of an animal subject the method including the administration to the animal a pharmaceutically effective amount of the polymer drug conjugate according to any preceding Claim.